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DYNAMICS OF ENDOTHELIAL FUNCTION INDICATORS IN PATIENTS WITH ARTERIAL HYPERTENSION WITH DIFFERENT CARDIOVASCULAR RISKS AGAINST THE BACKGROUND OF ANTIHYPERTENSIVE THERAPY

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Abstract. Dynamics of endothelial function in patients with arterial hypertension with different cardiovascular risk against the background of antihypertensive therapy. Pertseva N.O., Turlyun T.S., Sanina N.A. *The aim of the work was to investigate the dynamics of endothelial markers in patients with arterial hypertension with different cardiovascular risk under the influence of the prescribed treatment during a year of observation. The first group (with a moderate risk of cardiovascular events) included 48 patients with arterial hypertension (AH). The second group consisted of 54 patients with hypertension and a high risk of cardiovascular events, namely type 2 diabetes. Each group of patients was randomized into two subgroups by blood pressure (BP) medication. In patients of subgroup 1a (n=29) and subgroup 2a (n=35) – the main subgroups – the therapy necessarily included the angiotensin II receptor antagonist losartan potassium in a dosage of 50-150 mg/day, depending on the blood pressure level. Patients of subgroup 1b (n=19) and subgroup 2b (n=19) – comparison subgroups were treated with antihypertensive drugs of other first-line groups according to the data of the unified clinical protocol for the treatment of hypertension. According to the ROC analysis, it was determined that the dynamics of endothelin-1 (ET-1) indicators after 9 and 12 months of therapy (a decrease of 12% or more from the initial level) can predict the normalization of indicators of the coagulation and anticoagulation systems with indicators of sensitivity and specificity – 85% (95% CI 62.1-96.6%) and 92.9% (95% CI 76.5-98.9%), respectively. A decrease in the level of Willebrand factor (fV) by 23% or more due to such a treatment time can be used as a prognostic sign in determining the regression of endothelial dysfunction with sensitivity – 75% (95% CI 50.9-91.2%), specificity – 100% (95% CI 87.5-100%). According to the given data, both in the group with moderate and with high cardiovascular risk, there is a relationship between endothelial dysfunction (ED) and the duration of hypertension, indicators of the lipid spectrum and abdominal obesity – factors that increase the viscous resistance of the blood circulation, as well as platelet hyperactivity in the bloodstream. We have also established that according to the dynamics of ET-1 indicators after 9 and 12 months of therapy (decrease by 27% or more from the initial level), it is possible to predict the normalization of indicators of the coagulation and anticoagulation systems with indicators of sensitivity – 81.8% (95% CI 59.7-94.7%), specificity – 90.6% (95% CI 75-97.9%). A decrease in the level of fV by 24.5% or more after a year of treatment can be used as a prognostic sign in determining the regression of endothelial dysfunction with sensitivity – 68.2% (95% CI 45.1-86.1%), specificity – 71.9% (95% CI 53.3-86.2%). The obtained results testify to the dominant role of type 2 diabetes as a factor in platelet disorders of hemostasis. Taking into account the positive dynamics of the above-mentioned markers of ED during the year of treatment, their relationship with the reduction of blood pressure, indicators of the lipid spectrum and abdominal obesity, it should be noted the positive effect of angiotensin II receptor blockers (BRA II) as endothelioprotective drugs. Considering the irrefutable literary data about the absence of thrombomodulin in the blood stream, even its insignificant appearance indicates the presence of endothelial dysfunction. Determining the state and dynamics of changes in endothelial function under the influence of prescribed therapy will make it possible to improve the diagnosis of endothelial function disorders and increase the effectiveness of treatment of patients with hypertension and various cardiovascular risks.*

Реферат. Динаміка ендотеліальної функції у хворих на артеріальну гіпертензію з різним серцево-судинним ризиком на фоні антигіпертензивної терапії. Перцева Н.О., Турлюн Т.С., Саніна Н.А. *Метою роботи було дослідити динаміку ендотеліальних маркерів у хворих на артеріальну гіпертензію з різним кардіоваскулярним ризиком під впливом призначеного лікування впродовж року спостереження. У першу групу (з помірним ризиком серцево-судинних подій) увійшли 48 пацієнтів з артеріальною гіпертензією (АГ). Другу групу склали 54 пацієнти з АГ і високим ризиком серцево-судинних подій – а саме цукровим діабетом (ЦД) 2-го типу. Кожна група пацієнтів була рандомізована на дві підгрупи за лікарським засобом для корекції артеріального тиску (АТ). У пацієнтів 1а підгрупи (n=29) і 2а підгрупи (n=35) – основні підгрупи – у терапію обов'язково включали антагоніст рецепторів ангіотензину II лозартан калію в дозуванні 50-150 мг/добу залежно від рівня АТ. Пацієнтів 1б підгрупи (n=19) і 2б підгрупи (n=19) – підгрупи порівняння – лікували антигіпертензивними препаратами інших груп першої лінії згідно з даними уніфікованого клінічного протоколу лікування АГ. За даними ROC-аналізу визначено, що за динамікою показників ендотеліну-1 (ЕТ-1) через 9 і 12 місяців терапії (зменшення на 12% і більше від початкового рівня) можна прогнозувати нормалізацію показників згортальної та протизгортальної систем з показниками чутливості і специфічності – 85% (95% ДІ 62,1-96,6%) і 92,9% (95% ДІ 76,5-98,9%) відповідно. Зменшення рівня фактора Віллебранда (фВ) на 23% і більше через такий час лікування може використовуватися як прогностична ознака при визначенні регресу дисфункції ендотелію з чутливістю – 75% (95% ДІ 50,9-91,2%), специфічністю – 100% (95% ДІ 87,5-100%). За наведеними даними, як у групі з помірним, так і з високим кардіоваскулярним ризиком спостерігається взаємозв'язок ендотеліальної дисфункції (ЕД) із тривалістю АГ, показниками ліпідного спектра й абдомінального ожиріння – факторами, які підвищують в'язкісний опір кровообігу, а також гіперактивність тромбоцитів у кров'яному руслі. Нами встановлено також, що за динамікою показників ЕТ-1 через 9 і 12 міс. терапії (зменшення на 27% і більше від початкового рівня) можна прогнозувати нормалізацію показників згортальної та протизгортальної систем з показниками чутливості – 81,8% (95% ДІ 59,7-94,7%), специфічності – 90,6% (95% ДІ 75-97,9%). Зменшення рівня фВ на 24,5% і більше через рік лікування може використовуватися як прогностична ознака при визначенні регресу дисфункції ендотелію з чутливістю – 68,2% (95% ДІ 45,1-86,1%), специфічністю – 71,9% (95% ДІ 53,3-86,2%). Отримані результати свідчать про домінуючу роль ЦД 2-го типу як фактора тромбоцитарних порушень гемостазу. Враховуючи позитивну динаміку вищезазначених маркерів ЕД впродовж року лікування, їх зв'язок зі зниженням АТ, показників ліпідного спектра й абдомінального ожиріння, слід зазначити позитивний вплив блокатора рецепторів ангіотензину II (БРА II) в якості ендотеліопротективних препаратів. Зважаючи на неспростовні літературні дані про відсутність тромбомодуліну в нормі в кров'яному руслі, навіть незначна його поява свідчить про наявність ендотеліальної дисфункції. Визначення стану й динаміки змін ендотеліальної функції під впливом призначеної терапії дасть змогу вдосконалити діагностику порушень функції ендотелію і підвищить ефективність лікування пацієнтів з АГ та різним кардіоваскулярним ризиком.*

Arterial hypertension is a common multifactorial disease and the leading risk factor for the development of cardiovascular events, in particular, myocardial infarction, stroke, and renal failure [1]. Such pathogenetic mechanisms of hypertension as hyperactivation of the renin-angiotensin-aldosterone system and the sympathetic nervous system, hypertrophy, endothelial dysfunction, and oxidative stress are associated with changes in the platelet link of hemostasis. This primarily provokes platelet activation related to cardiovascular morbidity and mortality.

A series of clinical and morphological studies have proven that in patients with arterial hypertension, endothelial function undergoes significant damage even before the appearance of clinical and laboratory signs of disease complications and correlates with the degree of disorders of vascular and platelet hemostasis [2, 4, 10].

Compared to patients with normal blood pressure (BP), patients with arterial hypertension (AH) develop increased interaction of platelets and monocytes with endothelial cells, activate free radical oxidation processes, and damage the vascular endothelium, as a result of which endothelium-dependent vasodilation decreases [3, 5, 6].

A large number of markers of endothelial dysfunction (ED) and the possibility of drug influence on them, and therefore on the blood pressure level and the cardiovascular system as a whole, create a basis for developing a treatment strategy for each patient. Markers of endothelial dysfunction such as endothelin-1 (ET-1), thrombomodulin, and Willebrand factor (fV), along with the morphological analysis of blood cells, will be able to characterize various regulatory properties and critical changes in the vascular wall [4, 5, 7].

Objective – to investigate the dynamics of endothelial function in patients with arterial hypertension with different cardiovascular risks under the influence of antihypertensive treatment during one year of observation.

MATERIALS AND METHODS OF RESEARCH

All patients were stratified into two groups according to their cardiovascular risk based on the criteria of the European Society of Hypertension (ESC, 2023) [1]. The first group (with a moderate risk) included

48 patients with arterial hypertension without concomitant diseases. The second group consisted of 54 patients with hypertension and a high risk of cardiovascular events, which was determined by the presence of type 2 diabetes mellitus (DM) in all patients of this group. The number of patients with type 2 DM in the compensation stage was 37.0% (20 people), in the subcompensation stage – 63.0% (34 people). Decompensation of diabetes was an exclusion criterion.

Each patient group was further randomized into two blood pressure medication subgroups. Patients 1a (n=29) and 2a (n=35) – the main subgroups – were prescribed the angiotensin II receptor blocker (AR II) losartan potassium in a dosage of 50-150 mg/day. Patients 1b (n=19) and 2b (n=19) – comparison subgroups – were treated with antihypertensive drugs of other first-line groups according to the 2012 clinical guidelines for the treatment of hypertension without the use of ARB II [1, 7, 10]. If necessary, in the second group, the therapy was adjusted with other antihypertensive drugs, in particular, diuretics (indapamide or hydrochlorothiazide), calcium channel blockers (amlodipine), or β-adrenoceptor blockers (bisoprolol) to achieve BP targets. Angiotensin-converting enzyme (ACE) inhibitors (ramipril, lisinopril, perindopril) were prescribed only to patients of comparison subgroups (1b and 2b). Among patients in the first group, 100% of patients were on monotherapy with antihypertensive drugs, in the second group with high cardiovascular risk – 100% combined therapy with first-line antihypertensive drugs (65% – double and 35% – triple antihypertensive treatment).

The observation period began 12 months after patients were included in the study. A total of 4 visits took place: the first inclusion visit (0 months), followed by 6 (second visit), 9 (third visit), and 12 (the last, fourth visit) months.

The effectiveness of blood pressure control was carried out with the help of self-monitoring diaries. During all visits, the level of factors of endothelial dysfunction, namely endothelin-1 (ET-1), Willebrand factor (fV), and thrombomodulin, was determined in all patients by immunoenzymatic analysis. To assess the degree of endothelial marker disorders, a control group was created – 15 clinically healthy individuals, compared by age (average age 58.0±1.2 years; $p>0.05$) and gender (six men and nine women; $p>0.05$) [4, 5, 6, 7].

Statistical processing of research materials was carried out using biostatistics methods implemented in the STATISTICA v.6.1 (Statsoft Inc., USA) software package (license number AGAR909E415822FA) and MedCalc v.9.6.4.0. Under normal distribution, quantitative data are presented as arithmetic mean and standard error of the mean (M±m), Student's test was used to compare two samples. If the distribution differs from the average, the indicators are presented in the median and interquartile range (Me [Q25; Q75]). Cluster analysis and ROC analysis were also performed – to select subgroups with the best dynamics of ED markers and assess the prognostic significance of the factors determining these dynamics (area under the ROC curve AUC). The critical value of the level of significance (p) was taken to be <0.05, and a trend was noted at $p<0.10$ [8].

The study was approved by the bioethics commission of the Dnipro State Medical University "Dnipro State Medical University" (excerpt from protocol No. 17 of March 20, 2024) and was conducted per the written consent of the participants and following the principles of bioethics outlined in the Declaration of Helsinki "Ethical principles of medical research involving people" and the "General Declaration on Bioethics and Human Rights (UNESCO)." All subjects signed an informed consent to participate in the study.

RESULTS AND DISCUSSION

Throughout the study, all groups were homogeneous regarding all general clinical parameters. When analyzing the obtained data on the dynamics of indicators of the first group during the study, it was noted that in both subgroups, positive dynamics of blood pressure indicators was observed ($p<0.001$ compared to the initial level) (Table). All patients reached the target blood pressure values.

The significant effect of the treatment on the dynamics of blood pressure indicators in the analysis of data from patients with hypertension without concomitant pathology is regular. For changes in blood pressure, the coefficient of determination was $R^2=0.976$ ($p<0.001$), $R^2=0.596$ ($p<0.001$). That is, 97.6% of changes in SBP and 59.6% of DBP in patients with hypertension and moderate cardiovascular risk are associated with antihypertensive therapy. At the same time, the therapy scheme did not reliably affect the dynamics of these indicators [4, 7, 10].

After one year, the fV level decreased by 0.33 U/ml or by 28.9% compared to the initial level in patients of the 1a subgroup ($p<0.001$) and by 0.19 U/ml (by 15.8%) in the comparison subgroup ($p<0.05$). A significant decrease in the level of ET-1, starting from the 2nd visit, was noted only in subgroup 1a. Therefore, with comparable initial levels of ET-1 and fV in the subgroups ($p>0.05$), a significant difference in indicators is observed at the 4th visit – in patients receiving losartan potassium, the indicators are lower than in the subgroup with standard therapy. 21.4% of changes in ET-1 levels and 28.0% of fV production in blood serum are related to the treatment as a whole ($p<0.001$), another 13.5% and 15.6% of changes are due to the features of the applied antihypertensive regimen therapy based on losartan potassium.

Changes in blood pressure in patients of subgroups 1a and 1b under the influence of treatment during 12 months of the study

Indicator	Research period	1a (n=25)		1b (n=23)		p_1 between subgroups
		M±m	Δ, %	M±m	Δ, %	
Systolic blood pressure, mm Hg	1st visit (0 міс.)	167.2±0.92	-	166.5±0.76	-	t=0.56; p_1>0.05
	2nd visit (6 міс.)	139.2±0.62*	-16.3	141.2±0.53*	-15.2	t=1.62; p_1>0.05
	3rd visit (9 міс.)	137.1±0.67*	-18.0	137.7±0.56*	-17.3	t=0.70; p_1>0.05
	4th visit (12 міс.)	132.4±0.42*	-20.8	134.1±0.62*	-19.5	t=2.34; p_1<0.05
Diastolic blood pressure, mm Hg	1st visit (0 міс.)	78.8±1.76	-	80.7±1.64	-	t=0.75; p_1>0.05
	2nd visit (6 міс.)	77.2±1.67*	-2.0	78.8±1.71*	-2.4	t=0.70; p_1>0.05
	3rd visit (9 міс.)	75.9±1.60*	-3.7	77.1±1.66*	-4.5	t=0.54; p_1>0.05
	4th visit (12 міс.)	74.9±1.31*	-4.9	76.2±1.42*	-5.6	t=0.69; p_1>0.05

Notes: * – p<0.001 compared to baseline (1 visit) by Student's T-test for paired samples; Δ – changes in the indicator compared to the initial level in %; p_1 is the significance level of differences between subgroups according to the Student's t-test for unrelated samples.

A significant decrease in the level of thrombomodulin after one year of treatment was noted in the subgroup of patients who took ARB II (by 9.7%; p<0.05), while this indicator practically did not change in the subgroup on standard antihypertensive therapy.

As a result, according to cluster, correlation and ROC analysis, a subgroup of patients (n=20) with hypertension and the best dynamics of ED indicators was selected, that is a decrease in the level of ET-1 on average by (Me [LQ; HQ]) -29.5% [-47.9%; -15.7%]; thrombomodulin level – by -8.3% [-24.9%; 0.9%], the production of FV – by -38.3% [-73.9%; -20.7%] during the year of observation. The corresponding rates of decrease in indicators in other patients (n=28) were insignificant: changes in ET-1 level – by -2.1% [-5.1%; 2.6%] (p<0.001); thrombomodulin – by -3% [-5.6%; 1.4%] (p<0.05); fV – by -8.9% [-11.9%; -2.3%] (p<0.001). The best dynamics of ED indicators was associated with the use of drugs based on ARB II in therapy (AUC=0.739, rs=0.472; p<0.001), with the female gender of patients (AUC=0.668, rs=0.338; p<0.05), duration of hypertension less than five years (AUC=0.66, rs=0.293; p<0.05), as well as with a decrease in SBP to 133 mm Hg. (AUC=0.691, rs=0.374; p<0.01).

In addition, according to the data of the ROC analysis, it was determined that the dynamics of ET-1 indicators after 9 and 12 months of therapy (a decrease of 12% or more from the initial level) can predict the normalization of indicators of the coagulation and anticoagulation systems with indicators of sensitivity and specificity – 85% (95% CI 62.1–96.6%) and 92.9% (95% CI 76.5–98.9%), respectively. A decrease in the level of fV by 23% or more due to such a treatment time can be used as a prognostic sign in determining the regression of endothelial dysfunction with sensitivity – 75% (95% CI 50.9–91.2%), specificity – 100% (95% CI 87,5–100%).

When analyzing the data of patients with hypertension and high cardiovascular risk already before the second visit, i.e., after six months of therapy, the SBP level decreased (Table). The significant effect of antihypertensive treatment on the dynamics of blood pressure indicators is entirely natural: for changes in blood pressure, the coefficient of determination was R^2=0.804 (p<0.001), R^2=0.565 (p<0.001). That is, 80.4% of changes in SBP and 56.5% of DBP in patients with hypertension and high risk are related to therapy; another 10.9% and 6.3% of changes are due to the ARB II treatment regimen features.

During the study, in both subgroups with high cardiovascular risk, positive dynamics of fV indicators was observed (from p<0.05 to p<0.001 compared to the initial level): at the end of 12 months – 0.96±0.05 U/ml in the first and 1.08±0.07 U/ml in the second subgroup, without significant differences between them. The decrease in ET-1 levels at visits 3 and 4 was also statistically significant in both

subgroups but more pronounced on the background of ARB II therapy ($p<0.05$ between subgroups). Thrombomodulin also tended to decrease in both the main and comparison groups, with a more pronounced decrease during ARB II treatment – (2.88±0.19) ng/mL versus (3.00±0.25) ng/mL Jr. Changes in ET-1 levels by 25.2% ($R^2=0.252$) are associated with the treatment as a whole ($p<0.001$) and by 10.9% ($R^2=0.109$) – with the therapy scheme ($p<0.001$). The corresponding indicators for changes in the concentration of fV in blood serum during this observation period were 60.7% ($p<0.001$) and 2.8% ($p<0.01$). The indicator of the strength of the effect of the therapy on the variability of thrombomodulin values in high-risk patients was reliable ($R^2=0.130$; $p<0.001$) but did not depend on the treatment scheme ($R^2=0.027$; $p>0.05$).

According to the cluster analysis results, a group of 22 patients with the best dynamics of ED markers was selected, which turned out to be a decrease in ET-1 level on average by -47.1% [-67.0%; -28.8%]; thrombomodulin level – by -14.9% [-44.4%; -2.2%], fV level – by -27.0% [-31.8%; -20.8%]. The best dynamics of ED indicators correlated with the use of ARB-based drugs (AUC=0.702, rs=0.392; $p<0.01$), the duration of hypertension was less than eight years (AUC=0.268; $p<0.05$), as well as a decrease in SBP after 9 months of therapy (AUC=0.842, rs=0.001), after 12 months – up to 135 mm Hg (AUC=0.440; $p<0.001$), a decrease in the level of TG in the blood after 9-12 months up to 1.8 mmol/l (AUC=0.651, rs=0.310; $p<0.05$). Abdominal obesity is a factor that increases the viscous resistance of blood circulation, as well as the hyperactivity of platelets in the bloodstream. We have also established that according to the dynamics of ET-1 indicators after 9 and 12 months of therapy (decrease by 27% or more from the initial level), it is possible to predict the normalization of indicators of the coagulation and anticoagulation systems with indicators of sensitivity – 81.8% (95% CI 59.7-94.7%), specificity – 90.6% (95% CI 75-97.9%). A decrease in the level of fV by 24.5% or more after a year of treatment can be used as a prognostic sign in determining the regression of endothelial dysfunction, sensitivity – 68.2% (95% CI 45.1–86.1%), specificity – 71.9% (95% CI 53.3–86.2%).

Thus, analyzing the changes in blood pressure indicators in general during the entire study period, statistical differences in subgroups are observed only in the level of SBP after 12 months ($p<0.05$), but no clinically significant differences were noted. A more pronounced tendency to lower blood pressure in the main subgroup can be explained by a different trough: peak ratio (minimum/maximum action ratio) against the background of ARB II administration. It is also consistent with the results of many works, and the analysis of the dynamics of ED indicators showed a significant decrease in fV levels in both subgroups, starting from the second visit (from $p<0.05$ to $p<0.001$). The considerable effect of antihypertensive treatment on the dynamics of blood pressure indicators is entirely natural: for changes in blood pressure, the coefficient of determination was $R^2=0.804$ ($p<0.001$), $R^2=0.565$ ($p<0.001$). That is, 80.4% of changes in SBP and 56.5% in DBP in patients with hypertension and high risk are related to therapy, and another 10.9% and 6.3% of changes are due to the features of the ARB II treatment scheme used [3, 7, 10].

CONCLUSIONS

1. The obtained results indicate a higher prevalence of platelet disorders of hemostasis and endothelial dysfunction in hypertensive patients with a high risk of cardiovascular events due to type 2 diabetes compared to moderate-risk patients.
2. Our data obtained during the observation period have proven that even small concentrations of thrombomodulin in the blood plasma are likely markers of endothelial dysfunction.
3. Determination of such markers of the dynamics of endothelial function changes, such as ET-1, fV, and thrombomodulin, under the influence of antihypertensive therapy based on losartan potassium, makes it possible to improve the diagnosis of endothelial function disorders and increase the effectiveness of treatment of patients with arterial hypertension and various cardiovascular risks.

Contributors:

Pertseva N.O. – conceptualization, research, writing – review & editing;

Turlyun T.S. – research, formal analysis, writing – original draft;

Sanina O.N. – methodology, writing – review & editing.

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